Response to Therapy Following Retreatment of Serofast Early Syphilis Patients With Benzathine Penicillin

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Persistent nontreponemal titers after treatment are common among patients with early syphilis. We retreated 82 human immunodeficiency virus–negative early syphilis participants who were serofast at 6 months using benzathine penicillin. Only 27% exhibited serological response after retreatment and after an additional 6 months of follow-up.

Keywords. syphilis; serofast; retreatment; serological response.

Early syphilologists noted that "the effective treatment of early syphilis is one of the critical medical problems of modern times" [1]. A continuing challenge to determining the response to treatment of early syphilis is exemplified by the substantial proportion of patients who fail to achieve serological cure and remain serofast, defined as a <4-fold (2 dilution) decline in nontreponemal antibody titers at 6–12 months or as persistently low titers after treatment [2, 3]. Although retreatment is recommended for serofast patients if follow-up cannot be ensured, optimal management remains uncertain due to the paucity of data regarding serological response to retreatment and long-term outcomes.

We report results from a randomized, controlled clinical trial in which 21% of human immunodeficiency virus (HIV)–negative patients with early syphilis remained serofast 6 months after treatment [4]. We conducted additional analyses of data from this trial to determine the serological response of serofast patients after retreatment.

METHODS

Our randomized, controlled trial was conducted from June 2000 to March 2009 in North America and Madagascar and involved HIV-negative patients ≥18 years with early syphilis [4, 5]. The master protocol was approved by the University of Alabama at Birmingham (UAB) Institutional Review Board (IRB) and by IRBs serving each study site.

Eligibility criteria, procedures for enrollment and follow-up, and definitions for primary and secondary were previously described [4, 5]. Participants were diagnosed with early latent (EL) syphilis based on either a nonreactive syphilis serology or documented exposure to a sexual partner with primary or secondary syphilis within the preceding 12 months. All participants were required to have reactive rapid plasma reagin (RPR) antibody tests at enrollment. Participants without penicillin (PCN) allergy received initial treatment with 2.4 million units of intramuscular (IM) benzathine PCN or 2.0 g azithromycin (AZM) orally as directly observed therapy. RPR titers at the baseline visit prior to therapy and at the 6- and 12-month visits were performed at the UAB central laboratory according to standards [6].

Serological cure at 6 months following therapy was defined as either a negative RPR or ≥4-fold (2 dilution) decrease in titer. Seroreversion was defined as becoming RPR negative after therapy. Serofast status was defined as either no change in RPR titer or a 2-fold (1 dilution) decrease or increase in titer following initial therapy or retreatment. Per protocol, all participants determined to be serofast at 6 months after initial treatment with PCN or AZM were retreated with 1 dose of 2.4 million units of benzathine PCN IM at the 6-month visit.

These analyses were performed on the subset of the original per-protocol cohort who were serofast at 6 months after initial therapy, received retreatment, and had serological data at the 12-month visit. Proportions of participants with seroreversion, serological cure, or serofast status after retreatment were determined at 12 months using the definitions above. Participants who achieved serological cure after retreatment and those who remained serofast were compared for age and baseline and 6-month RPR titers using a Wilcoxon 2-sample test, and were

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compared for gender, geometric mean RPR titers, initial treatment regimen, and stage using a chi-square test.

RESULTS

We identified 82 HIV-negative adults with early syphilis who were serofast at 6 months after initial treatment with benzathine PCN (n = 41) or AZM (n = 41). Their median age was 29 years (range, 18–47), and most were male (55%), heterosexual (95%), and of Malagasy (88%) origin. Fourteen (17%) serofast participants had primary syphilis, 25 (31%) had secondary syphilis, and 43 (52%) had EL syphilis. At 6 months after initial treatment, the modal RPR titer among the 82 participants was 1:16 (n = 19, 23%), with a range from 1:1 to 1:1024.

After retreatment with benzathine PCN, only 11 (13%) participants exhibited a ≥4-fold decline in RPR titers from their 6-month titers, and 71 (87%) remained serofast at 12 months ($P < .0001$). However, when serological response was determined relative to baseline titers before initial treatment, 22 (27%) participants had achieved serological cure and 60 (73%) were serofast ($P < .0001$). Of those with serological response following retreatment, only 2 had seroreversion to a nonreactive RPR at the 12-month follow-up.

Gender, age, stage of syphilis, and initial treatment regimen were not associated with likelihood of achieving serological cure after retreatment (Table 1). However, there were statistically significant differences in the baseline and 6-month RPR titers between patients with serological cure vs serofast status. The median baseline RPR titer among the former was 1:32 compared with the median baseline titer of 1:8 among serofast patients ($P < .01$). There were similar differences in RPR titers at the 6-month visit between groups; participants with serological cure had a higher median RPR titer prior to retreatment than did participants who remained serofast at 12 months (Table 1). Furthermore, geometric mean RPR titers were significantly different between patients with serological cure vs serofast status at baseline and at 6 months (Table 1).

Table 1. Characteristics and Serological Outcomes of Serofast Patients With Early Syphilis Retreated With Benzathine Penicillin

	Outcome at 12 Months After Initial Treatment (ie, 6 Months After Retreatment)	
Characteristic	Seroreversion/Cure (n = 22)	Serofast (n = 60)
Gender (n, % male)	13, 59%	32, 53%
Age (25th, 50th, and 75th percentiles)	23, 25, 36	23, 30, 36
RPR titers (25th, 50th, and 75th percentiles)		
Baseline	1:16, 1:32, 1:128	1:4, 1:8, 1:32*
6 months	1:16, 1:32, 1:64	1:4, 1:8, 1:16**
RPR titers (geometric mean titer [95% CI])		
Baseline	34 (19, 62)	10 (8, 14)***
6 months	26 (13, 52)	8 (6, 11)****
Syphilis stage (n, %)		
Primary	5, 23%	9, 15%
Secondary	6, 27%	19, 32%
Early latent	11, 50%	32, 53%
Initial treatment (n, %)		
Penicillin	12, 55%	29, 48%
Azithromycin	10, 46%	31, 52%

Abbreviations: CI, confidence interval; RPR, rapid plasma regain.

Wilcoxon 2-sample test: *$P = .0004$; **$P = .001$. T test: ***$P = .0002$; ****$P = .0005$.

DISCUSSION

Despite retreatment with 2.4 million units benzathine PCN, 73% of patients with early syphilis who failed to achieve serological cure at 6 months after initial therapy remained serofast at 12 months. Patients with early syphilis who had higher nontreponemal titers at baseline and at 6 months (≥1:32) were more likely to exhibit serological cure after retreatment than those with lower titers. Among the patients who were serofast at 6 months, only a small proportion exhibited seroreversion after retreatment. Our findings illustrate the minimal improvement in serological response among serofast patients retreated with a single dose of PCN, especially those with lower RPR titers (≤1:16) at baseline or prior to retreatment.

Assessing the biological significance of the serofast state is difficult; stable nontreponemal antibody titers following therapy could represent persistent low-level infection with *Treponema pallidum*, variability of host response to infection, or possibly other confounding nontreponemal inflammatory conditions in the host. Nontreponemal tests measure immunoglobulin M (IgM) and IgG antibodies to *T. pallidum* and potentially to lipoidal and cardiolipin material released from damaged host cells during syphilis infection, which may also result from other illnesses that can produce tissue damage [7]. Although nontreponemal antibody titers generally correlate with syphilitic stage/disease activity [3], the implications of high titers (eg, 1:32) vs low titers in the serofast state are unknown. However, consistent with our previous analyses [4], these findings suggest that higher nontreponemal titers at retreatment are associated with a higher probability of serological response to therapy.

Clinical management of patients who remain serofast after treatment or retreatment for early syphilis is challenging. Treatment failure, which is usually defined as a sustained

4-fold increase in nontreponemal titers after therapy, is considered to be an indication for cerebrospinal fluid (CSF) examination for *T. pallidum* involvement [3]. However, some experts also recommend CSF examination for patients who do not demonstrate serological response after treatment (≥4-fold decrease in nontreponemal test titer or sustained seroreversion occurring within 6 months of treatment) [6]. Following these recommendations, 60 participants (13% of the 465 participants in the original study) [4] who remained serofast despite retreatment would have been considered for lumbar puncture to rule out neurosyphilis.

Our study provides the first evaluation of serological outcomes following retreatment of participants with the syphilis serofast state. However, we provided only 1 dose of benzathine PCN for retreatment, although the recommended therapy for patients with suspected treatment failure is 2.4 million units of benzathine PCN weekly for 3 weeks unless neurosyphilis is present [3]. We had a modest sample size of persons who received retreatment, and we did not conduct CSF examinations of serofast patients at the 12-month visit. However, none of the participants available for follow-up exhibited symptoms suggestive of neurosyphilis during the study period. Only 23 of our participants who were serofast at 12 months returned for additional follow-up at 18 and 24 months after initial treatment, which limited further analysis. Long-term outcomes after retreatment require further investigation, as does the applicability of our observations to persons with syphilis and HIV co-infection. Another limitation of our data is the lack of a comparison group by which to determine the expected decline in nontreponemal titers among serofast patients in the absence of retreatment. Thus, we cannot rule out that the seroreversion/serological cure exhibited by 24% of our participants may have been due to the natural decline in RPR titers after initial therapy, rather than due to the additional dose of benzathine PCN.

Prior to our study, there had been no evidence that patients who fail to exhibit an appropriate 4-fold decline in titers should receive additional courses of therapy for syphilis, though this is often done in clinical practice. Our results suggest that the incremental benefit of retreating HIV-negative serofast patients with early syphilis is marginal, considering the 1:3 ratio of serological response to serofast state at follow-up despite retreatment. Further, prospectively designed studies are needed; and our findings provide a starting point for addressing the unresolved questions about the serofast state and its management. At present, the management of individual serofast patients will continue to require clinical judgment, consideration of nontreponemal antibody titers, underlying medical conditions such as HIV infection, and/or the likelihood that the patient will return for subsequent serological monitoring after treatment.

Notes

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All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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